Development of an immune tolerant hESC source for allogeneic cell therapy applications

Grant Award Details

Development of an immune tolerant hESC source for allogeneic cell therapy applications

Grant Type: Transplantation Immunology

Grant Number: RM1-01711

Project Objective: The objective for this period was to assess the efficacy a novel non-viral-based gene delivery construct containing an engineered tolerogenic molecule that confers immune protection to cells expressing it on their extracellular membranes.

Investigator:

Name:	Basil Hantash
Institution:	Escape Therapeutics, Inc
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,453,040

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Development of an immune tolerant hESC source for allogeneic cell therapy applications

Public Abstract: Human embryonic stem cells (hESCs) are an ideal tissue source for cell replacement therapy (CRT). They have the potential for limitless self-renewal while retaining their ability to differentiate into a wide variety of cells and tissues. Since their first derivation in 1998, hESCs have been used in many studies in order to evaluate their potential therapeutic utility in humans. These have included animal models of myocardial infarction, Parkinson's disease, spinal cord injury, and bone marrow deficiency. Results so far have been promising, and many groups are advancing studies in support of clinical trials of hESC-derived cells. However, these studies have depended on either the use of immunosuppressed animals to avoid allogeneic or xenogeneic graft rejection or the coadminstration of highly toxic immunosuppressive drugs. Thus, a key limitation in transplanting hESC-derived cells remains their potential to elicit a host immune response with subsequent graft rejection due to immune mismatch between host and donor cells. In fact, recent studies showed that a single minor histocompatability antigen mismatch led to the rejection of allogeneic ESCs. In order to realize the enormous clinical promise of hESCs, novel cell lines capable of evading immune rejection by immunocompetent hosts are desperately needed. Our team has been focused on addressing this critical unmet need, and has had preliminary success in developing and validating an immune override mechanism for human adult stem cells and somatic cells. We accomplished this by engineering a tolerogenic molecule that confers immune protection to cells expressing it on their extracellular membranes. The short-term objective of our proposal is to determine whether engineering this override mechanism into hESCs leads to immune tolerance in a series of in vitro studies of allorecognition and in vivo studies of allorejection. Our long-term objective is the development of universal hESCs that overcome the immunological barrier without the stringent requirement for allelic matching, adjunctive immunosuppresssion, or autologous sourcing. This milestone would lead to a significant resolution to one of the key translational barriers impeding the use of hESC as a pluripotent stem cell source for CRT today. Our cutting edge project engages seasoned translational stem cell scientists and physicians, as well as CIRM-trained stem cell biologists whose collective expertise covers all the critical areas required for execution of this proposal. If successful, our project will provide the basis for creating a platform immune tolerant hESC technology that can be employed for the future development of regenerative medicine and curative therapies.

Statement of Benefit to California:	California has the largest population (~40M) of any state in the US and carries a substantial burden in annual healthcare expenditures. Cardiovascular, musculoskeletal, and neurodegenerative diseases, as well as stroke, diabetes and skin wounds represent some of the leading causes of disabilities, illnesses and death in California. The socioeconomic burden of these diseases is substantial and impacts California's overall standard of wellness, advancement, and prosperity. California has been at the forefront of advances in biotechnologies and medicine, offering some of the best healthcare in the world to its population, the nation, and the world. Recognizing the broad potential of stem cell research and its impact on human well-being and healthcare costs, Californians voted to pass Proposition 71 which led to creation of the California Institute of Regenerative Medicine (CIRM). Our proposal is in line with the aims of CIRM which supports innovative and translational stem cell research and development that can potentially transform medicine through curative rather than band-aid therapies, thereby improving healthcare delivery and costs for Californians and others. Immune rejection of administered human stem cells remains the most important limitation for advancing stem cell-based therapies to the clinical setting, and our aim has been to overcome this obstacle. Our team has developed and validated a mechanism for overriding immune rejection of human adult stem cells and somatic cells, and now plans to create human pluripotent stem cells that similarly evade immune rejection responses of the host. If successful, our newly engineered cells could serve as a platform for overcoming the key translational barrier confronting stem cell research today. By making this platform available to other commercial and research entities, our platform technology can help fuel the transformation of healthcare. Such a transformation would take place because it would finally become a reality that human stem cells can serve as a source to derive any cell or tissue required for creating curative therapies in an off-the-shelf manner, i.e. without the need for immunosuppression, stringent tissue matching, or autologous sourcing. By enabling translation of stem cells, it can be expected that a significant amount of new start-ups would form in California, spurring new opportunities for jobs and reigniting the nascent regenerative medicine industry. Besides its enormous potential to improve the health of California residents, our breakthrough would also inevitably lead to licensing opportunities as well as FDA-approved CRTs, both of which would generate significant future revenues for the State of California. Together, these outcomes would ensure that the generous financial support of CIRM by California taxpayers will lead to substantial benefit to California and its residents.

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